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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
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37 C.F.R. § 1.8

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February 7, 2002 — Thomas M. Boyce
Date — Thomas M. Boyce

AMENDMENT AND

RESPONSE TO THE OFFICE ACTION DATED NOVEMBER 7, 2001

Commissioner for Patents
Washington, D.C. 20231

Sir:

This paper is submitted in response to the Office Action ("the Action") dated November 7, 2001, for which the three-month date for response is February 7, 2002. No fees are believed due in connection with this paper. However, should any fee be required in any matter concerning the present application, please consider this paragraph a request and authorization to withdraw the appropriate fee under 37 C.F.R. §§ 1.16 to 1.21 from Fulbright & Jaworski L.L.P. Account No.: 50-1212/10022802/TMB.

Reconsideration of the application is respectfully requested.

I. AMENDMENTS

In the Claims:

Please cancel claims 8, 17, and 22 without prejudice or disclaimer.

Please amend the claims as follows:

Sub B1

1. (Amended) A method comprising:

a) obtaining at least a first anti-nuclease antibody;

b) obtaining at least a second anti-nuclease antibody;

c) obtaining a composition; and

d) admixing the anti-nuclease antibodies and the composition to form an admixture;

wherein nucleases that may be present in the admixture are inhibited.

A1

2. (Amended) The method of claim 1, wherein admixing is further defined as comprising mixing the first and second anti-nuclease antibodies to form a nuclease inhibitor cocktail and mixing the nuclease inhibitor cocktail with the composition.

3. (Amended) The method of claim 1, wherein obtaining the first and second anti-nuclease antibodies comprises obtaining a nuclease inhibitor cocktail comprising the first anti-nuclease antibody and the second anti-nuclease antibody.

4. (Amended) The method of claim 1, wherein the admixture comprises at least one nuclease.

5. (Amended) The method of claim 1, wherein the admixture comprises RNA.

6. (Amended) The method of claim 1, wherein the admixture is further defined as an *in vitro* translation reaction mixture, a transcription reaction mixture, a reverse transcription reaction mixture, or a coupled transcription/translation reaction mixture.

A1

7. (Amended) The method of claim 1, wherein the composition is a reagent used in molecular biology.

8. (Cancelled)

9. (Amended) The method of claim 1, wherein the first anti-nuclease antibody is a polyclonal antibody.

10. (Amended) The method of claim 1, wherein the first anti-nuclease antibody is an anti-ribonuclease antibody.

11. (Amended) The method of claim 10, wherein the first anti-ribonuclease antibody binds to one or more of RNase A, a member of the RNase A family, RNase B, RNase C, RNase 1, RNase T1, RNase T2, RNase L, a member of the RNase H family, a member of the angiogenin RNase family, eosinophil RNase, a micrococcal nuclease, a member of the mammalian ribonuclease 1 family, a member of the ribonuclease 2 family, a messenger RNA ribonuclease, 5'-3' exoribonuclease, 3'-5' exoribonuclease, a decapping enzyme, a deadenylase, RNase P, RNase III, RNase E, RNase I,I*, RNase HI, RNase HII, RNase M, RNase R, RNase IV, F; RNase P2,O, PIV, PC, RNase N, RNase II, PNPase, RNase D, RNase BN, RNase T, RNase PH, OligoRNase, RNase R, RNase Sa, RNase F1, RNase U2, RNase Ms, or RNase St.

A2

12. (Amended) The method of claim 10, wherein the first anti-ribonuclease antibody is an anti-RNase A antibody and the second anti-ribonuclease antibody is an anti-RNase 1 antibody.

13. (Amended) The method of claim 10, wherein the first anti-ribonuclease antibody is an anti-RNase 1 antibody and the second anti-ribonuclease antibody is an anti-RNase T1 antibody.

14. (Amended) The method of claim 10, wherein the first anti-ribonuclease antibody is an anti-RNase T1 antibody and the second anti-ribonuclease antibody is an anti-RNase A antibody.

A2

15. (Amended) The method of claim 1, wherein the first anti-nuclease antibody is an anti-deoxyribonuclease antibody.

16. (Amended) The method of claim 1, wherein the first anti-nuclease antibody binds to S1 nuclease or micrococcal nuclease.

17. (Cancelled)

18. (Amended) The method of claim 1, wherein at least a third anti-nuclease antibody is obtained and admixed with the first and second anti-nuclease antibodies and the composition.

A3

20. (Amended) The method of claim 1, comprising obtaining a nuclease inhibitor and admixing the nuclease inhibitor with the composition wherein the nuclease inhibitor is human placental ribonuclease inhibitor, a bovine ribonuclease inhibitor, a porcine ribonuclease inhibitor, diethyl pyrocarbonate, ethanol, formamide, guanidinium thiocyanate, vanadyl-ribonucleoside complexes, macaloid, sodium dodecyl sulfate, ethylenediamine tetraacetic acid, proteinase K, heparin, hydroxylamine-oxygen-cupric ion, bentonite, ammonium sulfate, dithiothreitol, β-mercaptoethanol, cysteine, dithioerythritol, tris (2-carboxyethyl) phosphene hydrochloride, Mg^{+2}, Mn^{+2}, Zn^{+2}, Fe^{+2}, Ca^{+2}, or Cu^{+2}.

A4

22. (Cancelled)

A5

23. (Amended) The method of claim 1, further defined as a method of inhibiting nucleases in the admixture.

A6

44. (Amended) The method of claim 37, wherein the anti-nuclease antibody binds to S1 nuclease or micrococcal nuclease.

A7

46. (Amended) The method of claim 45, further defined as comprising obtaining a nuclease inhibitor cocktail comprising at least the anti-nuclease antibody and the second nuclease inhibitor and placing the cocktail in the *in vitro* translation reaction.

Please add the following new claims:

A8

51. (New) The method of claim 18, wherein the third anti-nuclease antibody binds to one or more of RNase A, a member of the RNase A family, RNase B, RNase C, RNase 1, RNase T1, RNase T2, RNase L, a member of the RNase H family, a member of the angiogenin RNase family, eosinophil RNase, a micrococcal nuclease, a member of the mammalian ribonuclease 1 family, a member of the ribonuclease 2 family, a messenger RNA ribonuclease, 5'-3' exoribonuclease, 3'-5' exoribonuclease, a decapping enzyme, a deadenylase, RNase P, RNase III, RNase E, RNase I,I*, RNase HI, RNase HII, RNase M, RNase R, RNase IV, F; RNase P2,O, PIV, PC, RNase N, RNase II, PNPase, RNase D, RNase BN, RNase T, RNase PH, OligoRNase, RNase R, RNase Sa, RNase F1, RNase U2, RNase Ms, or RNase St.

52. (New) The method of claim 47, further comprising obtaining at least a third anti-nuclease antibody and placing the at least a third anti-nuclease antibody in the in vitro translation reaction.

53. (New) The method of claim 52, wherein the third anti-nuclease antibody binds to one or more of RNase A, a member of the RNase A family, RNase B, RNase C, RNase 1, RNase T1, RNase T2, RNase L, a member of the RNase H family, a member of the angiogenin RNase

family, eosinophil RNase, a micrococcal nuclease, a member of the mammalian ribonuclease 1 family, a member of the ribonuclease 2 family, a messenger RNA ribonuclease, 5'-3' exoribonuclease, 3'-5' exoribonuclease, a decapping enzyme, a deadenylase, RNase P, RNase III, RNase E, RNase I,I*, RNase HI, RNase HII, RNase M, RNase R, RNase IV, F; RNase P2,O, PIV, PC, RNase N, RNase II, PNPase, RNase D, RNase BN, RNase T, RNase PH, OligoRNase, RNase R, RNase Sa, RNase F1, RNase U2, RNase Ms, or RNase St.

A8

54. (New) The method of claim 52, wherein the at least a first anti-ribonuclease antibody is an anti-RNase A antibody, the at least a second anti-ribonuclease antibody is an anti-RNase 1 antibody, and the at least a third anti-ribonuclease antibody is an anti-RNase T1 antibody.

55. (New) The method of claim 5, wherein the RNA is produced in the admixture.

The claims marked for amendment are provided in Appendix A. For the Examiner's convenience, a clean copy of the pending claims as they stand amended is provided in Appendix B.

REMARKS

II. STATUS OF THE CLAIMS

Claims 1-50 were filed with the application. Claims 1-23 and 37-49 were elected in response to the restriction requirement of September 14, 2001. Claims 8, 17 and 22 are canceled without prejudice or disclaimer. Claims 1-7, 9-16, 18, 20, 23, 44 and 46 are amended. New claims 51-55 are added by the present amendment. Therefore, claims 1-7, 9-16, 18-21, 23, 37-49, and 51-55 are pending. Applicants note that the numbering and dependencies of the pending claims may require correction upon allowance. However, Applicants have retained the original claim numbering so as to simplify discussion of the Action.

III. THE REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH ARE OVERCOME

Claims 6, 11, 16 and 44 are rejected as indefinite under 35 U.S.C. §112, second paragraph. The Action states that it is not clear how a composition can be equivalent to a reaction. Applicants respectfully note that common parlance in the field of molecular biology is to refer to a particular mixture of reaction components and diluents, *e.g.* an *in vitro* translation reaction, as simply "a reaction." Nevertheless, in the interests of furthering prosecution, Applicants have amended claims 6, 11, 16, and 44 to recite reaction mixtures.

The Action states that the phrase "capable of" renders claims 11, 16, and 44 indefinite. Applicants have amended the claims to recite "binds to."

Applicants respectfully submit that the rejections are overcome.

IV. THE REJECTIONS UNDER 35 U.S.C. §102 ARE OVERCOME.

Claims 1-5, 7, 20, and 23 are rejected under 35 U.S.C. §102(b) as anticipated by Lee *et al.*, Immunochemistry, (1972), Vol. 9, pages 210-213. Applicants respectfully traverse the rejection. Applicants respectfully submit that Lee *et al.* does not disclose all the elements of the claims.

However, in the interest of speeding prosecution of the present case, Applicants have amended the claims to introduce the subject matter of claims 8 and 17 into the limitations of claim 1. Claims 1-5, 7, 20, and 23 now include the specific limitations of obtaining at least a first anti-nuclease antibody, obtaining at least a second anti-nuclease antibody and admixing the anti-nuclease antibodies and a composition to form an admixture wherein nucleases that may be present are inhibited.

Applicants respectfully submit that Lee *et al.* (1972) does not disclose all the elements of the present invention and therefore cannot anticipate the claims. At the least, Lee *et al.* (1972) does not disclose at least a second anti-nuclease antibody. Applicants therefore respectfully submit that the rejections are overcome.

V. THE REJECTIONS UNDER 35 U.S.C. 103(A) ARE OVERCOME.

A. The rejections of claims 1-5, 7-11, 20, 22, and 23 under 35 U.S.C. §103(a) over Lee et al. are overcome.

The Action rejects claims 1-5, 7-11, 20, 22, and 23 under 35 U.S.C. §103(a) over Lee *et al.* Claim 8 has been cancelled without prejudice or disclaimer by the present amendment. Its rejection is therefore moot. Applicants respectfully traverse the remaining rejections. "To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." See MPEP §2143.03. The Lee *et al.* reference does not teach or suggest all the limitations of the present claims. At the least, Lee *et al.* (1972) does not disclose at least a second anti-nuclease antibody as is presently claimed. Applicants therefore respectfully submit that the rejections are overcome.

B. The rejections of claims 1-5, 7-12, 20, 22, and 23 under 35 U.S.C. §103(a) over Lee et al. in view of Bucala (2000) are overcome.

The Action rejects claims 1-5, 7-12, 20, 22, and 23 under 35 U.S.C. §103(a) over Lee *et al.* in view of Bucala (2000). Claim 8 has been cancelled without prejudice or disclaimer, and its limitations are now included in claim 1. Applicants respectfully traverse the rejections.

The Action suggests that one of skill in the art would be motivated to combine the anti-RNase antibody of Bucala (2000) with the alleged teachings of Lee *et al.* to result in a method of

inhibiting nucleases. But contrary to the argument of the Action, RNase activity, *per se*, is never at issue in the Bucala reference. Indeed, the quoted passage from Bucala itself expressly teaches away from such a combination. In the Bucala reference, RNase proteins are described merely as indicators of the extent of dimerization promoted by glycotoxins. Bucala used rabbit anti-RNase A, ***conjugated to HRP*** to detect ***denatured*** RNase proteins in a western blot. Bucala therefore expressly did not use anti-RNase A antibodies effective in inhibiting active RNase activity.

First, the anti-RNase antibodies of Bucala are employed only when ***conjugated to HRP***, i.e. in a molecular form for reporting protein presence. This molecular form is clearly not simply anti-RNase antibodies. Furthermore, that "the samples were subjected to SDS-PAGE under reducing conditions" indicates to one of skill in the art that the RNase proteins are effectively ***denatured*** before blotting and detection. There is no suggestion that the particular rabbit anti-RNase A antibodies used, conjugated to HRP, would be at all effective in inhibiting active, non-denatured RNases. Yet, this is an express limitation of the claims. To wit, claim 1 reads "wherein nucleases that may be present in the admixture are inhibited."

Furthermore, no reference is provided to suggest the application of un-modified, non-conjugated anti-RNase A antibodies results in any inhibition of RNases in any context whatsoever. Since the references do not provide all the claimed elements of the present invention, Applicants respectfully submit that a valid *prima facie* case of obviousness against the rejected claims has not been made. In any event, neither Bucala nor Lee *et al.* provide for at least a second anti-nuclease antibody as presently claimed. Applicants respectfully submit that the rejection is overcome.

C. The rejections of claims 1-5, 7-11, 13, 14-20, 22, and 23 under 35 U.S.C. §103(a) over Lee et al. in view of Cazenave (1977) are overcome.

The Action rejects claims 1-5, 7-11, 13, 14-20, 22, and 23 under 35 U.S.C. §103(a) over Lee *et al.* in view of Cazenave (1977). Claims 8, 17 and 22 have been cancelled without prejudice or disclaimer, and their subject matter included as limitations of claim 1. Applicants respectfully traverse the rejections. Applicants respectfully submit that the rejections are based upon an incorrect interpretation of the disclosure of Cazenave (1977).

First, the antibodies to ribonuclease disclosed in Cazenave are not disclosed to be directed to RNase 1. Rather, the antibodies created and disclosed by Cazenave are directed to an unspecified ribonuclease. These antibodies are designated "Ab1" to indicate that they are the first antibodies to be used in experiments directed to dissecting the idiotype regulation of antibody synthesis in rabbits. The "1" appended to the "Ab" solely indicates that status, not the identity of the ribonuclease to which the antibody reacts. See page 5122, Column 2, second and third paragraphs, and Figure 1.

Second, the "Ab2" and "Ab3" antibodies are antibodies that react against the Ab1 and Ab2 antibodies, respectively. Thus, Ab2 does not recognize or react with any ribonuclease. Rather, Ab2 recognizes and reacts with Ab1. Likewise, Ab3 does not recognize or react with any ribonuclease. Ab3 recognizes and reacts with Ab2. See page 5122, Column 2, second and third paragraphs, and Figure 1. Therefore, neither Ab2, nor Ab3 can be construed in any sense to be ribonuclease inhibitors. Rather, they are carriers of idiotypes indicative of antibody responses. See the Discussion of Cazenave, generally.

Third, the Ab1′ antibodies are antibodies synthesized by the same rabbits that had produced Ab3 antibodies to the Ab2. See Cazenave at page 5122, Column 2, paragraphs 2 and 3.

Cazenave posits that the similarities of the idiotypes of Ab1′ antibodies produced among these rabbits are a result of the idiotypic relationships and similarities of immune response and allotype among individual rabbits. It is this phenomenon, the idiotypic relationships of the various antibodies, that is disclosed by Casenave. No mixture of anti-ribonuclease antibodies, let alone anti-RNase 1 antibodies is ever disclosed.

Lastly, Casenave relates the personal communication of J. Urbain to the effect that similar results relating to the idiotypic relationships. But, as explicitly stated by Cazenave in the cited passages (page 5124, Column 1, second paragraph) the antibodies were created to *Micrococcus* ***carbohydrates***. To quote: "They have obtained ***anti-carbohydrate*** Ab1′ antibodies bearing idiotypic specificities similar to those of original ***anti-carbohydrate*** Ab1 antibodies." (Emphasis added.) There is no mention of micrococcal nuclease anywhere in the reference, and certainly not at the cited passage.

In sum, a proper reading of the Cazenave reference reveals that it does not disclose equivalent second and third nuclease inhibitors as anti-ribonuclease antibodies. There are, in fact, no mixtures of anti-RNase 1 antibodies disclosed by Cazenave, nor any mention of Micrococcal anti-ribonuclease. Cazenave, therefore, does not disclose the limitations of the claims and cannot be part of a *prima facie* case of obviousness against the present claims. Applicants respectfully submit that the rejection is overcome.

D. The rejections of claims 1-11, 20-23, and 37-49 under 35 U.S.C. §103(a) over Lee et al. in view of Murphy et al. (1995) are overcome.

The Action rejects claims 1-11, 20-23, and 37-49 under 35 U.S.C. §103(a) over Lee *et al.* in view of Murphy *et al.* (1995). Claim 8 has been cancelled without prejudice or disclaimer.

The limitations of claim 8 are included in present claim 1. Applicants respectfully traverse the rejections.

Present claims 1-5, 7, 20, and 23 include the specific limitations of obtaining at least a first anti-nuclease antibody, obtaining at least a second anti-nuclease antibody and admixing the anti-nuclease antibodies and a composition to form an admixture wherein nucleases that may be present are inhibited. Applicants respectfully submit that neither Lee *et al.* nor Murphy *et al.* disclose or suggest the use of at least a second anti-ribonuclease antibody as presently claimed.

The Murphy *et al.* reference does not disclose the use of two antibodies in any situation, and most especially not in *in vitro* translation reactions. Indeed, Murphy *et al.* does not disclose the use of any antibodies whatsoever. Furthermore, there is no suggestion in Lee *et al.* that antibodies would work as inhibitors of nucleases in the reaction conditions of an *in vitro* transcription or other reaction mixture beyond that disclosed by Lee. Therefore, there is no basis for an artisan of ordinary skill to conclude from these references that the addition of anti-ribonuclease antibodies to a reaction mixture such as an *in vitro* transcription reaction would perform as desired.

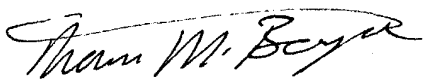
In fact, Murphy *et al.* discloses that "An extremely important feature of a RNase inhibitor" for use in such reactions is "that it remain fully functional under the various conditions to which RNA may be subjected." See Murphy *et al.*, under "Reaction Parameters," first paragraph, lines 1-3. Yet, there is no demonstration or suggestion in either of Lee *et al.* or Murphy *et al.* that anti-ribonuclease antibodies could withstand the various conditions as disclosed in the Murphy *et al.* reference. Absent such a suggestion from either reference and from the knowledge of one of skill in the art, Murphy *et al.* only teaches away from the present invention in that the reference raises numerous barriers to be crossed before achieving a

successfully useful RNase inhibitor. That a reference teaches away is sufficient on its own to defeat a *prima facie* case of obviousness, even if all the elements of the invention are shown to be available in the art. *Winner Int'l. Royalty Corp. v. Wang*, 202 F.3d 1340, 1349-50 (Fed. Cir. 2000). Applicants respectfully submit that no *prima facie* case of obviousness has been made against the claims because Murphy *et al.* leads the artisan away from the present invention in that Murphy *et al.* counters any reasonable expectation of success. Applicants therefore submit that the rejections are overcome.

VI. CONCLUSION

In light of the foregoing amendments and remarks, applicants respectfully submit that all claims are in condition for allowance, and an early indication to that effect is earnestly solicited. Should the examiner have any questions regarding this response, and call to the undersigned is invited.

Respectfully submitted,



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